UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,051	02/26/2004	Arthur M. Krieg	C1039.70083US06	8295

7590 03/22/2007

Helen C. Lockhart, Ph.D.
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,051	KRIEG ET AL.	
	Examiner	Art Unit	
	Oluwatosin Ogunbiyi	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-47* is/are pending in the application.

4a) Of the above claim(s) *34,36 in part,38,40 (in part) and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33,35,36 in part,37,39,40 (in part) and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/23/07, 2/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 10/16/2006 is acknowledged and has been entered into the record. Claims 1-27 have been canceled, claims 28-47 have been amended and claims 28-47 are now pending in the present application.

Election/Restrictions

Applicant's election with traverse of the species covalently linked, 5'-TGACGTT-3' and subcutaneous in the reply filed 1/25/07 is acknowledged. The traversal is on the ground(s) that that searching for other would not require an undue burden. This is not found persuasive because the species are distinct as set forth in the election requirement and a search for one specie will not overlap with a search for the other specie and therefore the search for each specie will be a serious burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Due to the species election requirement claims 28-33, 35, 36 (in part) 37, 39, 40 (in part), 42-47 are under examination. Claim 34, 36 (in part), 38, 40 (in part) and 41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected specie.

Information Disclosure Statement

The information disclosure statement filed 2/26/04 and 2/23/07 has been considered. An initialed copy is enclosed.

Claim Objections

Claim 28 is objected to because of the following grammatical error: The claim recites, "...comprising administering to a subject an oligonucleotides..." The claim should recite, "...comprising administering to a subject an oligonucleotide..." Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 28-33,35,36 (in part), 37, 39,40 (in part) 42,43 and 44-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-37,38-39,40,42, 43-46 of copending Application No. 10/787,737.

The claims are drawn to a method for preventing an immune system deficiency; comprising administering to a subject an oligonucleotide containing an unmethylated cytosine-guanine to prevent the immune system deficiency, wherein the oligonucleotide is stabilized.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treating a bacterial infection comprising administering to a subject having a bacterial infection a stabilized immunostimulatory oligonucleotide containing an unmethylated cytosine-guanine of the 10/787,737 application anticipates the instant method for preventing an immune system deficiency, comprising administering to a subject an oligonucleotide containing an unmethylated cytosine-guanine to prevent the immune system deficiency, wherein the oligonucleotide is stabilized. The 10/787,737 (and the instant specification) teaches that an immune system deficiency" shall mean a disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small cell), ovary, breast, prostate, colon, as well as other carcinomas and sarcomas) or a viral (e.g. HIV, herpes), fungal (e.g. *Candida* sp.), bacterial or parasitic (e.g. *Leishmania, Toxoplasma*) infection in a subject.

Thus the instant claims encompassing a method of treatment, prevention or ameliorating of an immune system deficiency are obvious over claims 28-37,38-39,40,42, 43-46 of copending Application No. 10/787,737.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2. Claims 28-31,32-33,35,37,40 (in part) and 42-46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 41-43,44, 45, 48-50, 53, 54, 55-58, 60, of copending Application No. 11/296,644 in view of Goodchild et al. 1990 Bioconjugate Chemistry volume 1, p. 165-187 and Draper et al, 1991, WO 91/12811.

The claims are drawn to a method for preventing an immune system deficiency; comprising administering to a subject an oligonucleotide containing an unmethylated cytosine-guanine to prevent the immune system deficiency, wherein the oligonucleotide is stabilized.

The 11/296,644 application is drawn to a method for stimulating an immune response in a subject comprising administering to a subject by intravenous or intraperitoneal route of administration a composition comprising a oligonucleotide delivery complex having an immunostimulatory CpG-containing oligonucleotide associated with a sterol or a lipid, in an amount effective to stimulate an immune response wherein the oligonucleotide is 8-100 bases in length, wherein the subject has an immune system deficiency, wherein the method is a method for treating an immune system deficiency, wherein the immune system deficiency is a viral infection, wherein the immune system deficiency is cancer or a tumor, wherein the tumor or cancer is eliminated.

11/296,644 does not teach that the immunostimulatory CpG containing oligonucleotides is stabilized by a phosphate backbone modification and in a pharmaceutical carrier.

Goodchild et al teach that modification to the ends and phosphate backbone of oligonucleotides are performed as they are the site of action of nuclease and also carry charges that inhibit cellular uptake. Goodchild teach that such modifications to the oligonucleotides are done when it is necessary for said oligonucleotides to survive in cell cultures or other biological environments and also to cross the cell membrane.

Draper et al teach the administration of oligonucleotides in a pharmaceutical carrier to subjects.

It would have been obvious to one of ordinary skill in the art at the time of the invention to stabilize the CpG containing oligonucleotides of the 11/296, 644 application as suggested by Goodchild et al because Goodchild et al teach that such modifications to the oligonucleotides are done when it is necessary for said oligonucleotides to survive in cell cultures or other biological environments and also to cross the cell

membrane thus resulting in the instant claimed invention with a reasonable expectation of success.

In addition to the obviousness set forth supra, the claims of 11/296,644 drawn to treatment of a viral infection or cancer or tumor are encompassed in the definition of immune system deficiency as set forth in the instant specification on p.11.

Furthermore, the 11/296,644 claims do not teach that the oligonucleotides is in a pharmaceutical carrier but it would have been obvious to administer the 11/296,644 oligonucleotide in a pharmaceutical carrier suitable for administration to a subject as taught by Draper et al, 1991, WO 91/12811.

Finally, the 11/296,644 claims do not teach that the cytosine-guanine (CpG) of immunostimulatory oligonucleotides is unmethylated. The specification of the instant application and the '644 application teach that oligonucleotides in which any or all CpG dinucleotide is methylated would not produce an immune reaction when administered to a subject in vivo (p.22 lines 4-7). Therefore, since the '644 application is drawn to stimulating an immune response then the immunostimulatory CpG oligonucleotides of '644 is unmethylated.

This is a provisional obviousness-type double patenting rejection.

3. Claims 28-33,35 and 37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-22, 32,33,35,50-53,63-64,66,81,82, 86,87,97,98, 102, 103, of copending Application No. 10/613916 in view of Goodchild et al. 1990, Bioconjugate Chemistry volume 1, p. 165-187 and Oberhauser et al. 1992 Nucleic Acids Research vol. 20 p. 533-538 and Draper et al, 1991, WO 91/12811.

The claims are drawn to a method for preventing an immune system deficiency; comprising administering to a subject an oligonucleotide containing an unmethylated cytosine-guanine to prevent the immune system deficiency, wherein the oligonucleotide is stabilized.

The 10/613,916 claims set forth above are drawn to a method for treating a mycobacterial infection in a subject, the method comprising: administering to a subject an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide, in an amount effective to treat or ameliorate an infection with a Mycobacterium bacterium, thereby treating the infection in the subject, wherein the bacterium is M. tuberculosis.

10/613,916 does not teach that the immunostimulatory CpG containing oligonucleotides is stabilized by a phosphate backbone modification and does not teach that said oligonucleotides is linked to a nucleic acid delivery complex.

Goodchild et al teach that modification to the ends and phosphate backbone of oligonucleotides are performed as they are the site of action of nuclease and also carry charges that inhibit cellular uptake. Goodchild teach that such modifications to the oligonucleotides are done when it is necessary for said oligonucleotides to survive in cell cultures or other biological environments and also to cross the cell membrane.

Oberhauser teach that oligonucleotides linked to phospholipids and cholesterol show an enhanced association with cultured cells and teaches that oligonucleotides thiocholesterol conjugates containing a bioreversible disulfide linkage have enhanced affinity for and internalization into cells (p. 533, left column under introduction).

Draper et al teach the administration of oligonucleotides in a pharmaceutical carrier to subjects.

It would have been obvious to one of ordinary skill in the art at the time of the invention to stabilize the CpG containing oligonucleotides of the 10/613,916 application as suggested by Goodchild et al and to link said oligonucleotides to a nucleic acid delivery complex such as a lipid or sterol as taught by Oberhauser et al because Goodchild et al teach that such modifications to the oligonucleotides are done when it is necessary for said oligonucleotides to survive in cell cultures or other biological environments and also to cross the cell membrane and Oberhauser et al teach that said complexes enhance the affinity of said oligonucleotides for and internalization into cells thus resulting in the instant claimed invention with a reasonable expectation of success.

In addition the obviousness set forth supra the claims of 10/613,916 drawn to treatment of a Mycobacterial infection are encompassed in the definition of immune system deficiency as set forth in the instant specification on p.11.

Furthermore, the 10/613,916 claims do not teach that the oligonucleotides is in a pharmaceutical carrier but it would have been obvious to administer the 10/613,916 oligonucleotide in any of the known pharmaceutical carriers suitable for administration to a subject as taught by Draper et al.

4. Claims 28-33,35 and 42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-32 of copending Application No. 11/645,106 in view of Goodchild et al. 1990 Bioconjugate Chemistry volume 1, p. 165-187 and Oberhauser et al. 1992 Nucleic Acids Research vol. 20 p. 533-538 and Draper et al, 1991, WO 91/12811.

The claims are drawn to a method for preventing an immune system deficiency; comprising administering to a subject an oligonucleotide containing an unmethylated cytosine-guanine to prevent the immune system deficiency, wherein the oligonucleotide is stabilized.

The 11/645,106 claims are drawn to a method of stimulating an immune response in a subject, comprising: identifying a subject that has or is at risk for having an immune system deficiency; and administering an isolated oligonucleotide comprising an unmethylated CpG sequence to the subject, to thereby stimulate the immune response in the subject wherein the subject has or is at risk for having a tumor or cancer, wherein the subject has or is at risk for having a bacterial infection.

The 11/645,106 claims does not teach that the oligonucleotides comprising an unmethylated CpG sequence is stabilized and/or linked to a nucleic acid delivery complex and is in a pharmaceutical carrier.

Goodchild et al teach that modification to the ends and phosphate backbone of oligonucleotides are performed as they are the site of action of nuclease and also carry charges that inhibit cellular uptake. Goodchild teach that such modifications to the

oligonucleotides are done when it is necessary for said oligonucleotides to survive in cell cultures or other biological environments and also to cross the cell membrane.

Oberhauser teach that oligonucleotides linked to phospholipids and cholesterol show an enhanced association with cultured cells and teaches that oligonucleotides thiocholesterol conjugates containing a bioreversible disulfide linkage have enhanced affinity for and internalization into cells (p. 533, left column under introduction).

Draper et al teach the administration of oligonucleotides in a pharmaceutical carrier to subjects.

It would have been obvious to one of ordinary skill in the art at the time of the invention to stabilize the CpG containing oligonucleotides of the 11/645,106 application as suggested by Goodchild et al and to link said oligonucleotides to a nucleic acid delivery complex such as a lipid or sterol as taught by Oberhauser et al because Goodchild et al teach that such modifications to the oligonucleotides are done when it is necessary for said oligonucleotides to survive in cell cultures or other biological environments and also to cross the cell membrane and Oberhauser et al teach that said complexes enhance the affinity of said oligonucleotides for and internalization into cells thus resulting in the instant claimed invention with a reasonable expectation of success.

In addition the obviousness set forth supra the claims of 11/645,106 drawn to treatment stimulating an immune response in a subject that has tumor or cancer or has bacterial infection are encompassed in the definition of immune system deficiency as set forth in the instant specification on p.11.

Furthermore, the 11/645,106 claims do not teach that the oligonucleotides is in a pharmaceutical carrier but it would have been obvious to administer the 11/645,106 oligonucleotide in a pharmaceutical carrier suitable for administration to a subject as taught by Draper et al.

Applicant(s) assistance is respectfully requested in specifically pointing other claims that might present similar double patenting issues as set forth above that are

present in the numerous applications filed by Applicant(s) especially in light of the broad definition of immune system deficiency in the instant specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-33, 35, 36 (in part) 37, 39, 40 (in part) and 42-47, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for treating, preventing or ameliorating an immune system deficiency, comprising administering to a subject an oligonucleotides containing an unmethylated cytosine-guanine to treat, prevent or ameliorate the immune system deficiency, wherein the oligonucleotide is stabilized.

The specification does not reasonably provide enablement for any method of treating, preventing or ameliorating an immune system deficiency comprising administering to a subject oligonucleotides containing an unmethylated cytosine-guanine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of immune system deficiency is broad and includes severe combined immunodeficiency syndrome, cell mediated immunity deficiency syndromes, X-linked

agammaglobulinaemia, antibody deficiency syndrome (see Herbet et al, The Dictionary of Immunology, page 89). Severe combined immunodeficiency is a disease in which both humoral and cell-mediated immunity are defective. In X-linked agammaglobulinaemia, there are low numbers of circulating B cells (i.e. mature) and of all immunoglobulin. Pre-B lymphocytes are present in normal numbers of the bone marrow. In this disease there is a single defect in a single gene encoding a protein tyrosine kinase. Cell mediated immunity deficiency syndromes are characterized by failure to express reactions of cell-mediated immunity (i.e. to reject an allograft, become sensitized to agents causing contact hypersensitivity, show delayed-type hypersensitivity reactions) and example include DiGeorge's syndrome, thymic hypoplasia and SCID. Antibody deficiency syndrome is characterized by low serum immunoglobulin levels and failure to produce antibody normally upon antigenic challenge. One, two or all three of the major classes of immunoglobulin (IgG, IgA and IgM) may be deficient. Antibody deficiency may exist in the presence of normal cell-mediated immunity. Types of antibody deficiencies are common variable immunodeficiency, IgA deficiency, IgG subclass deficiencies, X-linked agammagloublinaemia and X-linked hyper-IgM syndrome (see Herbet et al, The Dictionary of Immunology, pages 10, 33,141 and 166). Immune system deficiencies such as the primary deficiencies described above are caused by intrinsic or genetic defects in the immune system. The art does not recognize the prevention of such intrinsic or genetic defects in the immune system. However, therapeutic methods are available for primary immune system deficiencies and are geared towards immunoglobulin replacement therapy, haematopoietic stem cell transplantation (using bone marrow, cord blood or peripheral blood) and gene therapy (Cunnigham et al. 2005. Nature Review Immunology vol. 5 p.880-892).

Apart from the forms of primary immune system deficiency set forth above, there are secondary immune system deficiencies that are caused by infection e.g. viral infection or by chemicals e.g. HIV. As to prevention of a viral infection such as HIV in humans, prevention is currently geared towards prevention of mother to child transmission of the virus using antiviral drugs. In human adults, there are no

preventative vaccines or drugs for HIV infection and therapeutic methods are geared to existing infection.

The teachings of the specification are limited to in vitro data that demonstrate that unmethylated cytosine –guanine containing oligonucleotides stimulate B-cells and induce the production of cytokines and in vivo data that demonstrates in vivo induction of IL-6 in mice injected with said oligonucleotides. Production of IgM, natural killer cell activity and IL-6 by administering specific oligos containing the CpG DNA segment is not the same as any and/or all therapeutic effects (treating, preventing, ameliorating) in any and/or all subjects having an immune system deficiency which is broadly defined in the instant specification as a disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response such as to eliminate a tumor or cancer of brain , lung, ovary, breast, prostate, colon etc, or viral, fungal, bacterial or parasitic infection in a subject.

For primary immune system deficiencies, there is an absence or reduced numbers of T cells or mature B cells and plasma cells (Cunnigham et al). Therefore, administering the oligonucleotide of the present invention to subjects with such deficiencies who need a boost in their immune response will not result in the stimulation of B cells. Therefore, the treatment, ameliorating and prevention of such primary immune system deficiencies using oligonucleotides containing an unmethylated cytosine-guanine will not work since there is an absence of functioning B and T cells to start with. There is no empirical data reported in the specification at the time of filing showing efficacy of said oligonucleotides in any art- recognized model of immunodeficiency (either primary or secondary). Said oligonucleotide has not been demonstrated to provide treat, prevent or ameliorate, for example, class switching in order to provide for switching to specific isotypes (IgG1, IgG2, IgG3 and IgG4) or classes (IgA) to provide for a therapeutic effect on common variable immunodeficiency, IgA deficiency or IgG subclass deficiencies.

Furthermore, many bacteria and parasites are known to evade the immune system. For example, malaria parasites quickly infect liver cells within 5-10 minutes after they are injected by a mosquito, a far too short a time for the immune system to mount an efficient antibody response (Taubes et al. Science, October 2000, vol. 290 p. 435). The parasites go on to infect red blood cells where they are safe from both antibody and killer T-cell defenses. Therefore, for such a parasitic infection it is unpredictable whether the oligonucleotides of the present invention will be efficacious in treating or preventing such infection if the parasites are sequestered away from any boost in the immune response such as stimulation of B cells.

As to treating and ameliorating tumors, Kataoka et al (Jpn. J. Cancer Res vol. 83 p.244-247, 1992) show anti-tumor activity of synthetic oligonucleotides containing cytosine-guanine in a murine tumor system with sequences from cDNA encoding proteins of *Mycobacterium bovis* BCG. Said anti-tumor activity correlated with NK cell activity and interferon inducing activities. Although it appears that said oligonucleotide can treat preexisting tumor in the animal model it is unpredictable whether such oligonucleotides can prevent all types of cancer or tumors in other murine models of cancer or in humans. That is, can an oligonucleotide containing a cytosine-guanine act as a 'vaccine' to prevent all forms of cancers or tumors?

The instant specification fails to provide sufficient disclosure of any unmethylated cytosine-guanine oligonucleotide in the treatment, prevention or amelioration of an immune system deficiency in an animal or in a human. The specification does not predict or teach any positive therapeutic benefit (treating, preventing, or ameliorating) correlated with the administration of oligonucleotides containing an unmethylated cytosine-guanine either in a subject having any of the immune system deficiencies as defined in the specification. It is art recognized that for any novel therapy, the transition from the laboratory to the clinic (Petri dish experiments to animal experiments to bedside) is a quantum leap (Chatterjee et al. Cancer Immunol Immunother. 1994 38:75-82. Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in patients. Since the therapeutic indices of immunotherapeutic regimens can be species and model dependent it is not clear that

reliance on the in vitro and in vivo stimulation of B cells with unmethylated cytosine guanine oligonucleotides accurately reflects the efficacy of the claimed therapeutic strategy or prevention strategy based upon in vitro stimulation as disclosed in the specification. Furthermore, major considerations for any nucleic acid therapy protocol involve issues such as the amount of oligonucleotide administered, what amount is considered therapeutically effective , the route and time course of administration, sites of administration. For example, Gura (Science vol. 270 p. 575-577, 1995, see p. 576 right column) teach that synthetic oligonucleotides have caused side effects in experimental animals and that when administered by one-time injection in high doses, several phosphorothioates drugs were lethal to some of the animals. Furthermore, the oligonucleotides caused a transient decrease in two kinds of white blood cells as well as changes in blood pressure and heart rate. Such cardiovascular and other effects seen in animals can be minimized in patients using low does of the compounds and administering then gradually by continuous intravenous injection. Phosphorothioates have been found to accumulate in the liver, kidneys, and bone marrow of animals, although the long-term effects of this deposition are not clear (Gura).

It is therefore not clear that the skilled artisan could predict the efficacy of unmethylated cytosine guanine containing oligonucleotides encompassed by the claims for the treatment, prevention and amelioration of the broad scope of immune system deficiencies in a subject in view of the considerations set forth supra. Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the absence of working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510).

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 28, 29, 30, 37, 42, 43, 44, 45, 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Draper et al, 1991, WO 91/12811 as evidenced by Gura. Science vol. 270, p.575-577, 1995.

The claims are drawn to a method for treating, preventing or ameliorating an immune system deficiency, comprising administering to a subject an oligonucleotides containing an unmethylated cytosine-guanine to treat, prevent or ameliorate the immune system deficiency, wherein the oligonucleotide is stabilized.

Draper et al teach the therapeutic use of an oligonucleotide or oligonucleotide analog for treatment of herpes virus infection comprising administering to an animal or human said oligonucleotide which contains a cytosine-guanine (SEQ ID NO: 3,5,6,7 p.66) wherein said oligonucleotide is stabilized by a phosphorothioate phosphate

backbone modification (p.22 last bridging sentence, p.23 line 1-19, p. 66, 67 claims 19-26). Draper et al teach that said oligonucleotide or oligonucleotide analogs comprise 6 to 50 nucleotides in length. SEQ ID NO: 5,6,7 of Draper et al have two 5' purines and two 3' purines flanking a cytosine guanine. Claim 44 does not require that the two purines and two pyrimidines be directly juxtaposed to the cytosine and guanine and does not require them to be consecutive; the purines and pyrimidines just 'flank' the cytosine-guanine. Draper et al meet the limitation of the oligonucleotide comprising the motif of claim 45, 5' X1X2CGX3X4 3' wherein X1, X2,X3,X4 are nucleotides and a GCG trinucleotide sequence is not present at or near the 5' and 3' termini (See SEQ ID NO: 5,6,7). SEQ ID NO: 5 and 7 of Draper et al includes at least two cytosine-guanine motifs wherein one of the motifs is not palindromic e.g. GTCGTA. The antisense oligonucleotides and oligonucleotide analogs of Draper et al, which are synthesized (p. 27) are unmethylated as evidenced by Gura. Gura teach that antisense manufacturers don't add methyl groups to their synthetic oligonucleotides (p. 576 , middle column, third paragraph) and the synthesis described on p. 27-28 of Draper et al does not teach that methyl groups were added.

The instant specification on p. 11 defines immune system deficiency as a disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small cell), ovary, breast, prostate, colon, as well as other carcinomas and sarcomas) or a viral (e.g. HIV, herpes), fungal (e.g. *Candida* sp.), bacterial or parasitic (e.g. *Leishmania, Toxoplasma*) infection in a subject. Therefore, the method of therapeutic treatment of Draper et al meets the method of treatment of immune deficiency of the instant claims.

Claims 28, 29, 30, 31, 32,37, 39, 40 (in part),42,43,44 and 45-47 are rejected under 35 USC 102(e) as being anticipate by Hutcherson et al US 5,723,335 1998

(continuation of serial no 217,988, March 25, 1994) as evidenced by Gura. Science vol. 270, p.575-577, 1995.

The claims are drawn to a method for treating, preventing or ameliorating an immune system deficiency, comprising administering to a subject an oligonucleotides containing an unmethylated cytosine-guanine to treat, prevent or ameliorate the immune system deficiency, wherein the oligonucleotide is stabilized.

Hutcherson et teach a therapeutic or prophylactic treatment for bacterial, fungal, viral or oncogene derived infection in a host (column 6 line 12-30, column 7 line 45-55 comprising administering to a subject – animals or humans (column 5 line 20-35) antisense oligonucleotides containing a cytosine-guanine (column 6 line 12-30 and see sequence listing for SEQ ID 1, 2 and 3) wherein the oligonucleotides are stabilized by a phosphate back bone modification –phosphorothioate (column 6 line 12-30 and column 8 line 42-55). Hutcherson et al teach that liposomes and cationic lipids can significantly enhance the uptake of said oligonucleotides (column 8 line 54-55) and teach that said oligonucleotides may be administered by subcutaneous infection (column 7 last paragraph). Said oligonucleotides may be formulated in a pharmaceutical carrier (column 7 line 45-55) and can be 15-50 nucleotides in length (column 6 line 63-67). Hutcherson et al teach that the oligonucleotides comprise a cytosine and guanine flanked by two 5" purines (A, G) and two 3" pyrimidines (C,T) see for example SEQ ID NO:3. Claim 44 does not require that the two purines and two pyrimidines be directly juxtaposed to the cytosine and guanine and does not require them to be consecutive; the purines and pyrimidines just 'flank' the cytosine-guanine. SEQ ID NO: 2 and 3 of Hutcherson et al meet the limitation of the oligonucleotide comprising the motif of claim 45, 5' X1X2CGX3X4 3' wherein X1, X2,X3,X4 are nucleotides and a GCG trinucleotide sequence is not present at or near the 5' and 3' termini. SEQ ID NO: 2 of Hutcherson et al includes at least two cytosine-guanine motifs wherein one of the motifs is not palindromic e.g. GTCGTA. The antisense oligonucleotides of Hutcherson et al , which are synthesized, are unmethylated as evidenced by Gura. Gura teach that antisense manufacturers don't add methyl groups to their synthetic oligonucleotides (p. 576 ,

middle column, third paragraph) and the synthesis described example of Hutcherson et al does not teach that methyl groups were added.

The instant specification on p. 11 defines immune system deficiency as a disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small cell), ovary, breast, prostate, colon, as well as other carcinomas and sarcomas) or a viral (e.g. HIV, herpes), fungal (e.g. *Candida* sp.), bacterial or parasitic (e.g. *Leishmania, Toxoplasma*) infection in a subject. Therefore, the method of therapeutic treatment of Hutcherson et al meets the method of treatment of immune deficiency of the instant claims.

Status of the Claims

All claims under examination are rejected. Claim 28 is objected to. No claims allowed.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Jeffery Siew can be reached on 571-272-0787.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Oluwatosin Ogunbiyi
Examiner
Art Unit 1645

PATRICIA A. DUFFY
PRIMARY EXAMINER